II. REMARKS

Preliminary Remarks

Amendment of the claims

Claims 32, 37, 42, 47, 48, 54, 63, and 64, are amended, claims 41, 43, 58-60 and 65 are canceled, and new claims 67-72 are added.

Claims 32-40, 42, 44-57, 61-64, and 66-72 are currently pending.

Claims 32 and 37 are amended to specify a multivalent polymer that comprises a polymer backbone based upon monomer units selected from the monomer units identified in claims 43 and 65, which are canceled.

Claim 42 is amended to depend on claim 37.

Claims 47 and 48 are amended to depend on claim 46.

Claim 54 is amended for clarity; and claims 63 and 64 are amended to be directed to method of using the polymer modified biological element of claim 37.

New independent claims 67 and 68 are based on previous claim 35, and its base and intervening claims. New claim 68 is directed to the method of previous claim 35, including the limitations of previous claims 32 and 33, and new claim 67 is directed to a polymer modified biological element produced by said method.

New claims 69 and 70 are directed to a method of delivering a modified biological element to a cell of an individual, and depend respectively on independent claims 37 and 67.

New claims 71 and 72 are directed to a pharmaceutical composition comprising the polymer modified biological element of claims 37 and 67, respectively.

Patentability Remarks

Objections

The examiner objects to claim 35 as being dependent upon a rejected base claim, but has indicated that the claim would be allowable if re-written in independent form including all of the limitations of the base claim and any intervening claims.

In response, new independent claims 67 and 68 are submitted. New claim 68 is equivalent to previous claim 35 written in independent form, including all of the limitations of previous claims 32 and 33. New claim 67 is directed to the polymer modified biological element formed by the method of previous claim 35, and also includes all of the limitations of previous claims 32 and 33. In view of the indication in the official action that previous claim 35 would be considered allowable, it is respectfully submitted that new claims 67 and 68 are similarly allowable.

35 U.S.C. §112, first paragraph, written description

Claims 32-34, 36-42, 44-64, and 66 are rejected under 35 U.S.C. §112, first paragraph, for alleged failure to comply with the written description requirement. Claims 35, 43, and 65 were not included in the rejection. Reserving the right to pursue the broader claims in a continuation application at a later date, and while not agreeing with the allegation that the application fails to adequately describe the full scope of the invention, the independent claims of the application are amended to incorporate the subject matter of claims 35, 43, and 65, in order to expedite prosecution of the application. In particular, independent claims 32 and 37 are amended to specify a multivalent polymer comprising a backbone based on the monomer units identified in claims 43 and 65, and new independent claims 67 and 68 are amended to include the subject matter of previous claim 35 written in independent form and to include the limitations of previous claims 32 and 33. The applicant submits that the claims as amended satisfy the requirements for written description under 35 U.S.C. §112, first paragraph, and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

35 U.S.C. §112, first paragraph, enablement

Claims 58 to 60 are rejected under 35 U.S.C. §112, first paragraph, because the specification is not considered to enable one of skill in the art to make or use the invention as it relates to gene therapy. Without relinquishing the right to pursue the subject matter of the claims in a later filed continuation application, claims 58 to 60 are canceled.

Claims 32-34, 36-42, 44-57 61-64 and 66 are rejected under 35 U.S.C. §112, first paragraph, because the specification is enabling for embodiments where the backbone of the multivalent polymer is HPMA, HEG, or ethyleneglycol-oligopeptide backbone, as specified in claims 43 and 65, but is not considered to be enabling of other embodiments. Without relinquishing the right to pursue the subject matter of the claims in a later filed continuation application, and in order to expedite prosecution, independent claims 32 and 37 are amended to incorporate the subject matter of claims 43 and 65, which are canceled. Withdrawal of the rejection of claims 32-34, 36-42, 44-57, 61-64, and 66 under 35 U.S.C. §112, first paragraph, is therefore respectfully requested.

The applicant directs the examiner's attention to new claims 69 and 70, which are directed to methods of delivering a biological element to a cell *in vivo*, and are dependent on claims based respectively on previous claims 65 and 35. The methods do not refer to gene therapy, or require that a therapeutic benefit be conferred to the subject.

35 U.S.C. §101

Claims 60, 63, and 64 are rejected under 35 U.S.C. §101 as failing to be directed to a process or other patentable subject matter.

35 U.S.C. §112, second paragraph

Claims 60, 63 and 64 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite in failing to identify positive steps encompassed by the claims.

In response, claims 63 and 64 are amended to put them into method claim format. These claims now recite specific steps and thus are believed to be clear and not indefinite. Claim 60 is canceled. The applicant submits that claims 63 and 64 comply with the requirements of 35 U.S.C. §101 and §112, second paragraph, and respectfully requests that the rejections be withdrawn.

Claims 43, 47-49, 54, 64, and 65 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite, for the following reasons:

Claim 43 is considered indefinite because the precise meaning of "such as" is considered to be unclear. Claim 43 is canceled, and the words "such as" are not present in the amended claims.

Claims 47 and 48 are considered indefinite because there is no antecedent basis in claim 37 for "the biologically active agent." In response, claims 47 and 48 are amended to depend on claim 46, which provides the requisite antecedent basis.

Claim 54 is considered indefinite because the precise meaning of "an oleyl or other hydrophobic group" is considered to be unclear. In response, claim 54 has now been amended to refer to "an oleyl or a hydrophobic group." The meaning of the claim is now considered to be clear to one of skill in the art.

Claim 64 is considered indefinite because the precise meaning of "in the agricultural industry" is considered to be unclear. In response, claim 64 has to delete the expression "in the agricultural industry." The meaning of the claim is now considered to be clear to one of skill in the art.

Claim 65 is considered indefinite because it uses "or" in the Markush grouping. Previous claim 65 has been deleted, and the amended claims are not subject to this ground for rejection.

In view of the foregoing, withdrawal of the rejection of pending claims 47, 48, 54, and 64 under 35 U.S.C. §112, first paragraph, is respectfully requested.

Supplemental Experimental Data

The applicant submits herewith for the examiner's review experimental data which is considered to be evidence that one of skill in the art can follow the teachings of the application and successfully make and use the claimed invention without having to perform undue experimentation.

Targeting oncolytic virus to tumors in vivo

Oncolytic (tumor selective) viruses are able to infect a wide range of both normal and malignant tumor cells. However, selective replication of the virus is only permitted in tumor cells, due to the endogenous expression of cellular factors, which ultimately results in tumor cell destruction. This technology is well established and widely published in the literature.

Although selectivity with oncolytic viruses has been addressed and demonstrated at the intracellular level, technologies to provide selectivity at the point of infection have been in adequate. As a result, much of the virus that is administered is taken up by normal cells, thereby decreasing the amount available to the tumor and possibly causing unwanted toxicity.

Here we describe a polymer coating technology that masks the virus surface and prevents infection of both tumor and normal cells, and also allows selective targeting.

Appendix A, labeled Figure 1, is a graph that shows the results of an experiment in which adenovirus was coated with N-2-hydroxypropylmethacrylamide (HPMA) and then administered to mice. As can be seen, polymer coated virus is cleared from the blood much more slowly than control virus, which is not polymer coated, thus assisting delivery of the polymer coated virus to a target site. The coated virus, unable to infect normal cells, circulates for extended periods in the blood stream of mice.

Appendix B, labeled Figure 2, demonstrates selective virus infection of tumor cells *in vivo* following introduction of a tumor specific targeting ligand to the coating polymer. As explained in the figure legend, unmodified vaccinia virus shows widespread infection of organs and tissues throughout the body (lower frame). Polymer coated vaccinia shows no detectable expression in any part of the mouse (middle frame). Targeted virus shows transgene expression restricted to site of the tumour (upper frame). The targeting ligand targets heparin sulphates exposed during the inflammatory process that occurs within tumours. The small amount of expression in the tail may be caused by inflammation at the site of needle injection. Improved targeting in this way should decrease unwanted side effects and improve the therapeutic index. Targeting and delivery has been highlighted as the key hurdle prevents the effective employment of therapeutic biopharmaceuticals. Polymer modification is able to overcome this important barrier.

Appendix C, labeled as Figure 3. Data showing advantageous effects of polymer coating. Polymer modified virus particles demonstrating improved selectivity towards malignant tissues. Unlike unmodified adenovirus particles, adenovirus particles which are modified with reactive multivalent polymers based on HPMA are unable to infect normal cells via the natural pathways involving coxsackie and adenovirus receptor (CAR) and integrins. Blocking infection of normal cells therefore results in higher concentrations of virus particles remaining available to infect tumours. Tumour cells have a natural propensity for accumulation of particles by non-specific, fluid phase uptake. This process provides a mechanism for polymer modified adenovirus to preferentially enter and infect tumour cells more efficiently than normal cells. Figure 3 shows the results of polymer modified adenovirus administration into the peritoneal cavity of mice bearing SKOV3 tumours. The SKOV3 cells form multiple tumour nodules throughout the peritoneal cavity. The micrograph on the left is a light image while the one on the right shows the same field of view taken under fluorescent light. Virus activity was determined by expression of green fluorescent protein (GFP) engineered into the virus genome. The expression of GFP is restricted to the tumor with no significant expression in the normal tissue. Clinical trials involving intraperitoneal administration of adenovirus vectors which are not polymer modified have failed due to infection of non-target normal tissues.

III. CONCLUSION

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If the examiner identifies any points that he feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Please charge any fees or credit any overpayments associated with the submission of this response to Deposit Account Number 03-3975.

Respectfully submitted,

/thomas a cawley jr/

Date: July 26, 2006 By_____

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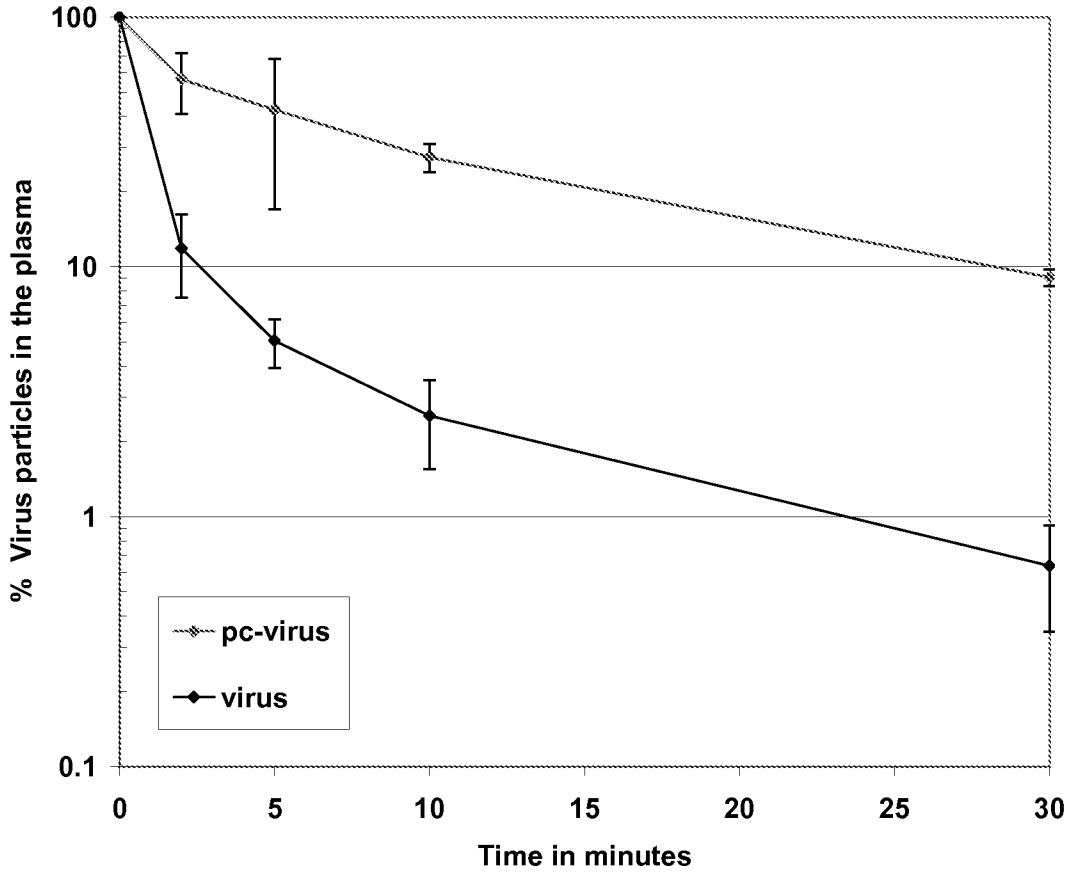
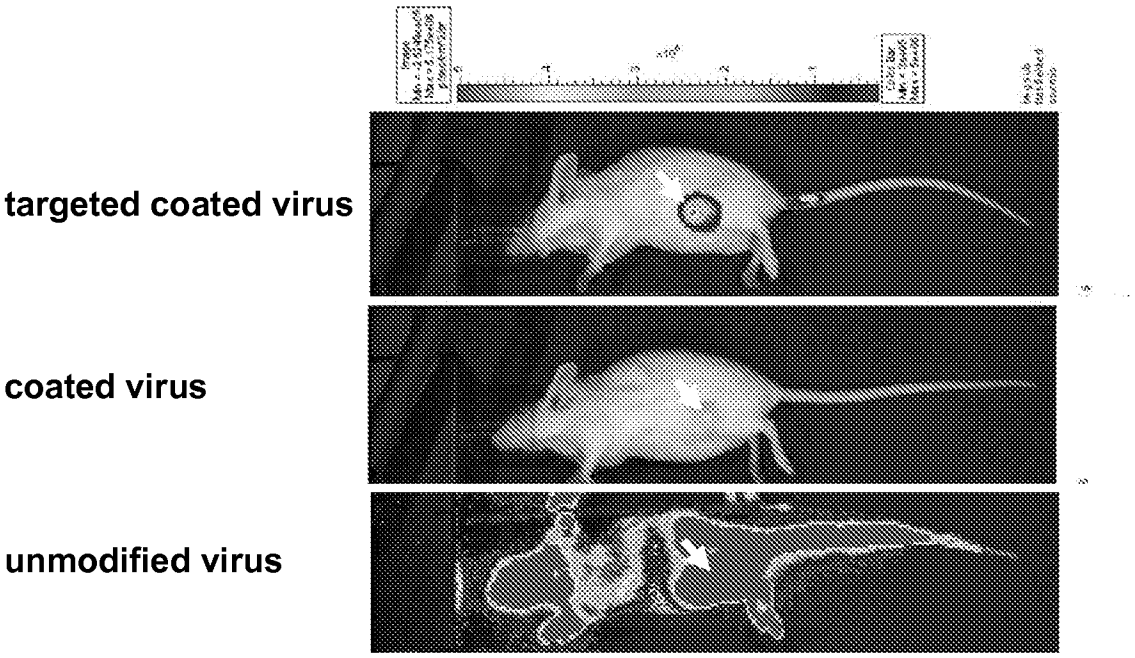
APPENDIX A


100
10
1
0.1
% Virus particles in the plasma
pc-virus
virus
0
5
10
15
20
25
30
Time in minutes

APPENDIX B


targeted coated virus
coated virus
unmodified virus

APPENDIX C

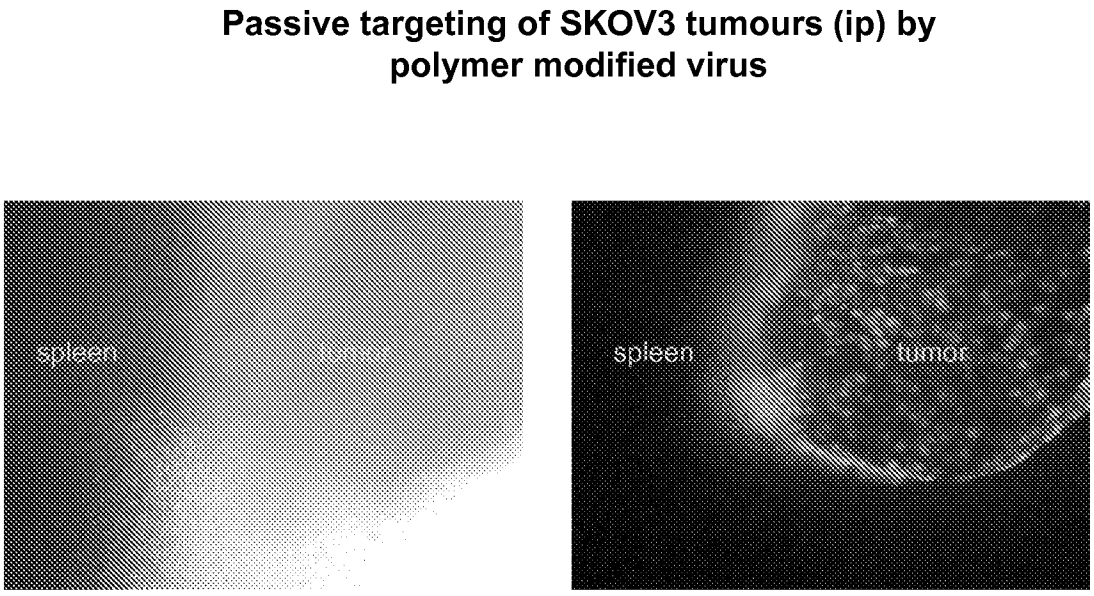


Figure 3. Polymer modified adenovirus particles expressing GFP demonstrating improved selectivity towards SKOV3 tumour growing in the peritoneal cavity of MF1nude mice.